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Preparation of 1-methyl-3-phenylisoquinoline derivatives from oximes using polyphosphoric esters

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We show a beneficial new approach to the preparation of 1-methyl-3-phenylisoquinoline derivatives. This method involves heating polyphosphate ester and the appropriate oximes obtained from 3,4-diphenylbut-3-en-2-one derivatives. The isoquinolines were synthesised in yields mainly ranging from about 50 to 70%, and their structures were confirmed by proton and carbon nuclear magnetic resonance spectroscopy and elemental analysis. This newly developed procedure is particularly suitable for the synthesis of 1-methyl-3-phenylisoquinoline derivatives with chlorine, methyl, and methoxy substituents on the aromatic ring.

Introduction

Plants containing various alkaloids based on the isoquinoline structure have been known for many hundreds of years and have been successfully used in medicine as drugs for different afflictions. Because of the high intensity and diversity of physiological activities, the syntheses of these compounds have become a very important aim in chemical science.[1–4] Among the many alkaloids containing isoquinoline structures, the most important of them belong to the opium group of compounds, including papaverine, an antispasmodic agent commonly used in medicine to decrease tension as well as the activity of smooth muscles.[5,6] Moreover, also used are some benzophenanthridine derivatives, *e.g.*, sangwinaryna or chelidonine.[7–12] Many alkaloids, particularly 3-phenylisoquinoline and its derivatives, demonstrate anticancer or antirheumatic activities and can prevent the symptoms of hypertension and neuralgia. It has been demonstrated that 1-(4-methylpiperazinyl)-3-phenylisoquinoline hydrochloride works as an anticarcinogenic agent against various types of cancer cells. Furthermore, the natural alkaloid known as Decumbenine b has been applied in medicine as a very effective drug against hypertension and neuralgia for many decades.[13–16]

In 1893, Bischler and Napieralski described a synthetic method for isoquinoline derivatives based on the cyclisation of phenylethylamides in the presence of phosphorus pentoxide as a dehydrogenation agent.[17] The Bischler–Napieralski reaction occurs according to a mechanism involving an intramolecular electrophilic substitution reaction between an aromatic ring and a nitrilium ion that is generated *in situ* from a reacting amide. The yield of the reaction depends on both the presence and the amount of electron donating groups in the aromatic ring containing the nitrogen atom.[18,19] From 1936–1941, Krabbe and co-workers studied a cyclisation reaction of *N*-styrylamide.[20–22] Later, Goszczyński and Zieliński investigated the effect of the *N*-styrylamide structure on their cyclisation ability in isoquinoline systems.[23] Subsequent research demonstrated that 1-methyl-3-phenylisoquinoline derivatives could not be obtained *via* the Pictet and Gams method. The cyclisation of 2-acetamido-1,2-diphenylethan-1-ol derivatives in boiling decalin with phosphorus pentoxide or chlorophosphoric acid at 150 °C resulted in the formation of 1-methyl-4-phenylisoquinoline derivatives instead of the expected products substituted with a phenyl group on the third carbon atom.[24]

Likewise, isoquinoline derivatives can be obtained from the unsaturated oximes of ketones and aldehydes without the need to isolate intermediate products. Thomas and coworkers described a synthesis of isoquinoline starting from an oxime of the cinnamic aldehyde in the presence of rare-earth metal ions implanted in zeolites. However, small quantities of byproducts (cinnamonitrile and cinnamaldehyde) were formed in the process and contaminated the reaction product.[25,26] The synthesis of isoquinoline derivatives can be performed in common solvents as well as in ionic liquids.[27–30]

The ethyl ester of polyphosphoric acid (polyphosphate ester, PPE) is a dehydrogenation agent containing cyclic esters and may be obtained from the reaction between phosphorus pentoxide and diethyl ether in the presence of chloroform. PPE is often used as a substitute for polyphosphoric acid (PPA) due to its better solubility in organic solvents and higher safety when used as a reagent in organic syntheses. Moreover, the reaction can be conducted under milder conditions; thus, PPE improves the economic viability of the synthesis.[31–33] PPE was successfully applied as a reagent in the

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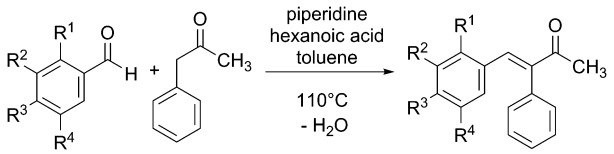
Beckmann rearrangement[31] and in the Bischer–Napieralski reaction.[18,19] Likewise, PPE can be applied in the Biginelli cyclocondensation reaction,[33] the Fischer indole synthesis,[34] alkylation or *N*-alkylation reactions,[35] and a bioparticle condensation.[36] In the presence of PPE, amino acids and peptides undergo conversions into macromolecular peptides.[36]

Results and discussion

The aim of this work was to develop a simple method to synthesise 1-methyl-3-phenylisoquinoline derivatives from the oximes of unsaturated ketones without separating *N*-styrylamides as intermediates. The structures of all synthesised compounds were confirmed by proton and carbon nuclear magnetic resonance spectroscopy, and product purity was determined by elemental analysis (CHN) and thin layer chromatography (TLC). 3,4-Diphenylbut-3-en-2-one derivatives were obtained *via* the condensation reactions of benzaldehyde derivatives with 1-phenylpropan-2-one followed by the dehydration of the formed hydroxy ketones (Scheme 1). A solution of the benzaldehyde derivative and 1-phenylpropan-2-one in toluene was heated in the presence of catalytic amounts of hexanoic acid and piperidine for 12 h.

Afterwards, all the required oximes were formed by the reaction of the 3,4-diphenylbut-3-en-2-one derivatives and hydroxylamine hydrochloride in an alkaline environment using methanol as solvent. Table 1 lists the yields and melting points of the oximes synthesised according to the reaction presented in Scheme 2. The oximes of unsaturated ketones were obtained in the form of crystals during the slow cooling of the post-reaction mixture with yields ranging from 51 to 90%.

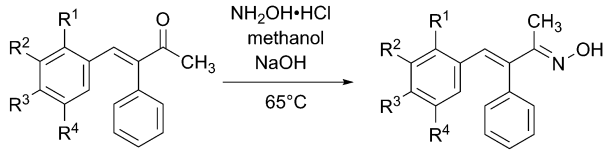
As a result of these studies, we found that heating the obtained oximes of 3,4-diphenylbut-3-en-2-one derivatives with



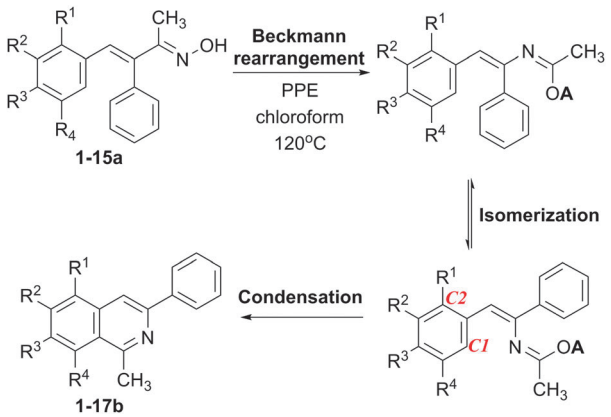
Scheme 1 The synthesis of 3,4-diphenylobut-3-en-2-one derivatives.

Table 1 Prepared oximes

Oxime	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1a	H	H	H	H	77	157–158
2a	CH_3	H	H	H	81	142–144
3a	H	CH_3	H	H	57	132–134
4a	H	H	CH_3	H	90	178–180
5a	Cl	H	H	H	87	138–140
6a	H	Cl	H	H	85	145–149
7a	H	H	Cl	H	80	193–194
8a	OCH_3	H	H	H	89	147–150
9a	H	OCH_3	H	H	74	132–136
10a	H	H	OCH_3	H	63	185–188
11a	OCH_3	OCH_3	H	H	81	182–187
12a	H	OCH_3	OCH_3	H	51	184–186
13a	OCH_3	H	OCH_3	H	55	194–196
14a	OCH_3	H	H	OCH_3	71	185–187
15a	H	OCH_3	H	OCH_3	51	166–168



Scheme 2 The synthesis of oximes from ketones.



Scheme 3 A proposed mechanism of isoquinoline synthesis, where A is a fragment of the PPE molecule.

polyphosphate ester at 120 °C leads to a formation of 1-methyl-3-phenylisoquinoline derivatives. This observation proves that three different reactions occur in the reaction mixture: Beckmann rearrangement, isomerisation of intermediates, and finally condensation. The proposed mechanism of this process is shown in Scheme 3.

An $|E|$ isomer of the amide should be formed in the rearrangement reaction of the selected oxime. However, this compound is not able to cyclise to an isoquinoline derivative due to the presence of the double bond, which is unable to rotate freely. In the presence of PPE as reaction medium, the isomerisation of the $|E|$ isomer of the amide to the $|Z|$ isomer occurs. However, all amides exist in the form of nitrylium cations in the reaction mixture, which strongly facilitates the cyclisation reaction. In order to confirm the assumed reaction mechanism, oximes **2a** and **11a** were heated with PPE at 70 °C for 5 min, and water was then slowly added to the post-reaction mixture. Thus, the mixture of isoquinoline and both amides was obtained, as confirmed by IR spectroscopy. In the spectrum of the resulting mixture, we identified the absorption bands from N–H (3200–3300 cm^{-1}) and C=O (1650–1700 cm^{-1}) stretching vibrations of an amide group.

Moreover, TLC analysis clearly proved that the post-reaction mixture consists of an isoquinoline structure and two isomers of the amide.

The oxime **4a** was used to determine the influence of reaction temperature on the efficiency of the synthesis. The mixture of the substrate and PPE was heated for 3 h at temperatures ranging from 100 to 140 °C (Table 2). The highest yield of isoquinoline was observed at 120 °C, and this temperature was selected to perform all syntheses. The deterioration of the reaction yield at temperatures

Table 2 PPE-catalysed synthesis of 1,7-dimethyl-3-phenylisoquinoline (**4b**) at various temperatures

No.	Temperature (°C)	Yield (%)
1	100	58
2	110	60
3	120	67
4	130	61
5	140	56

Table 3 Prepared isoquinoline derivatives

Product	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1b	H	H	H	H	68	47–48[a]
2b	CH_3	H	H	H	48	73–75
3b	H	CH_3	H	H	76	47–49
4b	H	H	CH_3	H	67	64–65
5b	Cl	H	H	H	45	60–61
6b	H	Cl	H	H	19	95–98
7b	H	H	Cl	H	47	99–100
8b	OCH_3	H	H	H	61	116–118
9b	H	OCH_3	H	H	72	132–134
10b	H	H	OCH_3	H	36	121–122
11b	OCH_3	OCH_3	H	H	71	109–112
12b	H	OCH_3	OCH_3	H	74	144–145
13b	OCH_3	H	OCH_3	H	13	154–156
14b	OCH_3	H	H	OCH_3	53	80–81
15b	H	OCH_3	H	OCH_3	77	116–118
16b	H	H	OH	H	5	275–278
17b	OCH_3	H	OH	H	10	151–154

[a] Mp 48 °C, ref. 37.

above 120 °C may be related to the decomposition of PPE, which is unstable at high temperatures. Table 3 shows that the yield depends on the type and position of the substituent on the phenyl group of the starting oxime. The unsubstituted 1-methyl-3-phenylisoquinoline **1b** (where R^1, R^2, R^3, R^4 = H) is known in the literature[23,37] and was obtained with a 65% yield from N-(1,2-diphenylvinyl)acetamide.[23] The location of a methyl group in the *para* position causes the cyclisation of the oxime to the isoquinoline **4b** with a similar yield (67%). However, when the methyl group was located in the *ortho* position, the isoquinoline **2b** was obtained with a lower efficiency (48%). This indicates that steric hindrance occurs during the cyclisation of oxime **2b** to this isoquinoline. The highest yield was observed for isoquinoline **3b**, in which the methyl group is substituted in the *meta* position (76%).

The yields of isoquinoline syntheses from oximes containing one methoxy group also depend on the location of this group on the phenyl substituent of the substrate. The oxime **8a** with the methoxy group in the *ortho* position undergoes transformation to the isoquinoline with a yield lower by about 11% than the oxime **9a** containing the methoxy group in the *meta* position, which was obtained in 72% yield. However, when the methoxy group was located in *para* position, isoquinoline **10b** was synthesised with the lowest yield – only 36%. Moreover, it was found that in addition to the expected main product, small amounts (5%) of 7-hydroxy-1-methyl-3-phenylisoquinoline (**16b**) were formed.

On the other hand, the presence of two methoxy groups in the oxime generally does not negatively affect the synthetic efficiency. As a result of transformation of oximes **11a** and **12a**, compounds **11b** (5,6-dimethoxy-1-methyl-3-phenylisoquinoline) and **12b** (6,7-dimethoxy-1-methyl-3-phenylisoquinoline) were obtained in yields of 71% and 74%, respectively. The exception was the synthesis of compound **13b**, which also contained two methoxy groups. The low yield of this reaction (13%) was caused by the formation of by-products (*e.g.*, 7-hydroxy-5-methoxy-1-methyl-3-phenylisoquinoline (**17b**)) during the reaction. A similar efficiency was observed for the cyclisation of oxime **6a**, wherein 6-chloro-1-methyl-3-phenylisoquinoline (**6b**) was obtained in only 19% yield. This also implies that the presence of a substituent that reduces the total electron density of the aromatic ring adversely affects the efficiency of the entire process. This phenomenon also confirms the yields of isoquinolines substituted with a chlorine in the *ortho* (**5b**) or *para* (**7b**) position, which reached similar values (slightly less than 50%).

The oximes **3a**, **6a**, **9a**, **12a** and **15a** may theoretically be converted into two different products, which are structural isomers. Scheme 3 shows that during the cyclisation of these five amides, the carbon of the carbonyl group can attack the carbon C1 as well as the carbon C2. The analysis of ^1H and ^{13}C NMR spectra revealed that only one of these reaction products was obtained. By comparing the location and multiplicity of the signals of the formed isoquinoline with the theoretical spectra of the two isomers, we discovered that the obtained products were formed by attack on the C1 carbon.

Further research proved that the use of other reagents such as phosphoryl chloride, phosphorus pentoxide, or chlorophosphoric acid instead of PPE does not result in the formation of isoquinoline structures from oximes. Moreover, the PPE is an effective condensing reagent only for oximes of ketones containing the aryl group on the third carbon atom in their structure. The reaction does not occur when this group is replaced with a hydrogen or alkyl group.

Conclusions

The ethyl ester of polyphosphoric acid (PPE) applied in our study proved to be an efficient reagent for the cyclisation of oximes to isoquinolines substituted by one or two functional groups. PPE allowed 1-methyl-3-phenylisoquinoline derivatives to be obtained with high efficiency and purity. Moreover, three different reactions, all of which are promoted by only one reagent, occur in the reaction mixture: Beckmann rearrangement, isomerisation and condensation. As a result, we eliminate the necessity of isolating the reaction intermediates as well as the use of various catalysts suitably selected for each reaction. The studied cyclocondensation reaction turned out to be a selective process; only one isomer of isoquinoline was formed as the result of all syntheses.

Experimental

General

Melting points were measured with a Büchi melting point B-540 apparatus. The IR spectra were collected using a Bruker FT-IR

EQUINOX 55 spectrophotometer. ^{1}H NMR and ^{13}C NMR analyses were performed on a Gemini Varian 300 VT spectrometer with tetramethylsilane as an internal standard. CHN elemental analyses were performed at the Adam Mickiewicz University, Poznan (Poland). The TLC chromatograms were obtained using KIESEGEL 60 GF_{254} plates and a mixture of toluene–ethyl acetate (1 : 1) as the mobile phase.

Synthesis of PPE

The reagent was prepared by refluxing a mixture of 150 g of phosphorus pentoxide (P_40_{10}), 150 mL of diethyl ether and 300 mL of chloroform until the solution was clear (15–30 h). The mixture was then filtered through glass wool and concentrated on a rotary evaporator. The obtained PPE was diluted with anhydrous chloroform to a density of 2.7 g mL^{-1} before use.

Condensation of 1-phenylprop-2-one with benzaldehyde derivatives

The appropriate benzaldehyde derivative (0.1 mol), 1-phenylprop-2-one (0.11 mol), toluene (100 mL) as a solvent and catalytic amounts of hexanoic acid and piperidine were added to a reaction flask. Next, the solution was heated in a Dean Stark apparatus for 12 h at 110 °C. The reaction mixture was cooled to room temperature, and toluene was evaporated under reduced pressure. The obtained raw product was recrystallised from ethanol.

Oximation of 3,4-diphenylbut-3-en-2-one derivatives

In a round-bottom flask, a selected ketone (0.05 mol) and hydroxylamine hydrochloride (0.08 mol) were dissolved in 50 mL of methanol. Afterwards, sodium hydroxide (0.06 mol) dissolved in aqueous–methanolic solution (1 : 1) was added into the reaction mixture. The solution was heated in a round-bottom flask equipped with a reflux condenser for 1 h. The obtained precipitate was filtered off under reduced pressure and recrystallised from ethanol.

General procedure for the synthesis of 3-phenylisoquinoline derivatives

The cyclisation of a selected oxime (0.02 mol) was carried out in a solution of PPE (0.035 mol) in chloroform at 120 °C for 3 h. The post-reaction mixture was acidified with hydrochloric acid, and both chloroform and contaminants were separated by steam distillation. Then, an excess of sodium hydroxide was added to the flask containing the isoquinoline hydrochloride in order to isolate of the reaction product. Next, the mixture was extracted three times with diethyl ether, and the organic phase was dried over sodium sulphate. Afterwards, the solvent was removed, and the crude product was recrystallised from ethanol.

In the synthesis of 7-methoxy-1-methyl-3-phenylisoquinoline (**10b**) and 5,7-dimethoxy-1-methyl-3-phenylisoquinoline (**13b**), the separated aqueous phase was acidified with a 10% solution of hydrochloric acid; as a result, by-products containing hydroxyl substituents (**16b**, **17b**) precipitated. The aqueous mixture was then extracted three times with diethyl ether, and the organic phase was dried over sodium sulphate. Afterwards, the solvent was removed.

1-Methyl-3-phenylisoquinoline (1b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–6.74 (10H, m), 2.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 150.0, 139.8, 136.5, 129.6, 128.6, 128.2, 127.5, 126.9, 126.6, 125.5, 115.1, 22.5; Anal. calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.44; H, 6.21; N, 6.12.

1,5-Dimethyl-3-phenylisoquinoline (2b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (2H, m), 8.04 (1H, s), 7.42 (6H, m), 3.05 (3H, s) 2.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149.9, 140.3, 136.1, 134.3, 130.4, 128.7, 128.2, 127.1, 126.5, 126.2, 111.7, 23.0, 19.0; Anal. calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.71; H, 6.33; N, 5.89.

1,6-Dimethyl-3-phenylisoquinoline (3b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (2H, m), 7.97 (1H, s), 7.43 (6H, m), 3.02 (3H, s) 2.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 149.9, 140.1, 137.0, 130.1, 129.9, 129.3, 127.0, 125.9, 126.8, 125.9, 115.9, 22.5, 21.7; Anal. calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.64; H, 6.55; N, 6.09.

1,7-Dimethyl-3-phenylisoquinoline (4b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (2H, m), 7.88 (1H, s), 7.38 (6H, m), 3.03 (3H, s) 2.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 149.2, 140.0, 137.0, 134.9, 132.1, 128.6, 128.1, 127.4, 126.8, 126.7, 124.5, 115.0, 22.6, 22.0; Anal. calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.45; H, 6.59; N, 6.14.

5-Chloro-1-methyl-3-phenylisoquinoline (5b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (1H, s), 8.18–7.39 (8H, m), 3.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 151.1, 139.5, 134.7, 132.0, 130.0, 128.8, 128.7, 127.5, 127.2, 126.4, 124.6, 111.4, 22.9; Anal. calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.61; H, 4.83; N, 5.59.

6-Chloro-1-methyl-3-phenylisoquinoline (6b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14–7.39 (9H, m), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 151.1, 139.3, 137.6, 136.1, 128.7, 128.6, 127.5, 127.3, 127.0, 126.2, 124.7, 114.1, 22.6; Anal. calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.58; H, 4.64; N, 5.62.

7-Chloro-1-methyl-3-phenylisoquinoline (7b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–7.36 (9H, m), 3.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 150.3, 139.3, 135.0, 132.2, 130.9, 129.2, 128.7, 128.5, 127.0, 126.9, 124.7, 114.5, 22.5; Anal. calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.80; H, 4.71; N, 5.67.

5-Methoxy-1-methyl-3-phenylisoquinoline (8b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): 8.36 (1H, s), 8.22–8.20 (2H, m), 7.65 (1H, m), 7.54–7.26 (4H, m), 6.97 (1H, m), 4.01 (3H, s), 3.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 155.2, 149.5, 140.1, 129.3, 128.6, 128.1, 127.2, 126.9, 126.5, 117.4, 109.4, 107.2, 55.6, 23.0; Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 6.01; N, 5.74.

6-Methoxy-1-methyl-3-phenylisoquinoline (9b). White cryst. solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–6.74 (9H, m), 3.91 (3H, s), 2.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 157.9, 150.6, 140.0, 138.8, 136.1, 128.6, 128.2, 127.8, 127.0, 122.2, 119.3, 114.7, 105.1, 55.4 22.5; Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.97; H, 6.14; N, 5.53.

7-Methoxy-1-methyl-3-phenylisoquinoline (10b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–8.09 (2H, m), 7.84 (1H, s),

7.50–7.24 (5H, m), 6.97 (1H, m), 3.95 (3H, s), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 156.8, 148.1, 139.7, 132.2, 129.2, 128.7, 128.0, 127.5, 126.7, 122.8, 115.1, 103.6, 55.4 22.6; Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.81; H, 6.23; N, 5.49.

5,6-Dimethoxy-1-methyl-3-phenylisoquinoline (11b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19–8.16 (3H, m), 7.90 (1H, d, J = 9.0 Hz), 7.86 (1H, m), 7.53–7.26 (3H, m), 4.02 (6H, m), 2.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 151.2, 150.1, 142.2, 140.1, 132.8, 128.6, 128.2, 127.1, 122.5, 114.5, 108.8, 61.2, 56.5, 22.7; Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.29; H, 6.23; N, 5.10.

6,7-Dimethoxy-1-methyl-3-phenylisoquinoline (12b). White cryst. solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–7.10 (8H, m), 4.04 (6H, m), 2.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 152.5, 149.7, 149.1, 133.4, 128.6, 127.6, 126.7, 122.2, 114.3, 105.6, 103.8, 55.9, 22.7; Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.52; H, 6.15; N, 4.97.

5,7-Dimethoxy-1-methyl-3-phenylisoquinoline (13b). Brown cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (1H, s), 7.65–7.21 (7H, m), 3.99 (3H, s), 3.96 (3H, s), 2.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 156.5, 156.2, 147.8, 140.0, 128.6, 127.9, 127.7, 126.8, 125.6, 109.8, 101.0, 95.2, 55.7, 55.4, 22.9; Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.64; H, 6.01; N, 4.85.

5,8-Dimethoxy-1-methyl-3-phenylisoquinoline (14b). White cryst. solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22–6.71 (8H, m), 3.96 (3H, s), 3.91 (3H, s), 3.19 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 151.8, 149.6, 148.7, 139.7, 131.4, 128.6, 128.2, 126.9, 119.5, 108.8, 107.4, 105.2, 55.8, 55.6, 28.9; Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.23; H, 6.28; N, 5.30.

6,8-Dimethoxy-1-methyl-3-phenylisoquinoline (15b). White cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.15–8.12 (3H, m), 7.71 (1H, s), 7.52–7.37 (4H, m), 3.92 (6H, m), 3.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 159.4, 157.8, 150.3, 140.1, 139.7, 128.5, 128.2, 126.8, 115.6, 114.3, 98.9, 97.8, 55.4, 55.3, 28.6; Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.11; H, 5.87; N, 5.14.

7-Hydroxy-1-methyl-3-phenylisoquinoline (16b). Yellow cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.40 (1H, s), 7.59–7.37 (9H, m), 2.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 177.1, 159.5, 139.0, 133.3, 132.3, 129.3, 129.2, 128.7, 127.6, 121.0, 119.9, 111.2, 19.0; Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.79; H, 5.21; N, 5.75.

7-Hydroxy-5-methoxy-1-methyl-3-phenylisoquinoline (17b). Yellow cryst. solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.33 (1H, s), 7.67–7.28 (6H, m), 6.17 (2H, m), 4.07 (3H, s), 2.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.5, 178.5, 168.9, 166.4, 136.9, 134.5, 132.0, 130.8, 128.1, 127.8, 119.0, 117.7, 112.4, 57.7, 18.8; Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.23; H, 5.99; N, 4.94.

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